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## **Psychopharmacological Advances in Eating Disorders**

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**Abstract**

Anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) are the primary eating disorders (EDs). The only psychopharmacological treatment options for EDs with approval in some countries include fluoxetine for BN and lisdexamfetamine for BED. Given the high comorbidity and genetic correlations with other psychiatric disorders, it seems possible that novel medications for these conditions might also be effective in EDs.

The current scientific literature has increased our understanding of how medication could be beneficial for patients with EDs on a molecular, functional and behavioral level. On the basis of theoretical considerations about neurotransmitters, hormones and neural circuits, possible drug targets for the treatment of EDs may include signal molecules and receptors of the self-regulatory system such as serotonin, norepinephrine and glutamate, the hedonic system including opioids, cannabinoids and dopamine and the hypothalamic homeostatic system including histamine, ghrelin, leptin, insulin, and glucagon-like peptide-1.

The latest research points to an involvement of both the immune and the metabolic systems in the pathophysiology of EDs and highlights the importance of the microbiome. Therefore, the next few years may unveil drug targets for EDs not just outside of the brain, but possibly even outside of the human body.

## 1. Introduction

### 1.1. Historical preliminary remarks

Despite decades of clinical experience and research in the field of eating disorders (EDs), the prognosis for patients with EDs is still poor. For example, a recent cohort study showed that only 30% of patients with anorexia nervosa (AN) have recovered after 9 years [1].

If we take a look at the broader history of psychiatry from the start of the 19<sup>th</sup> century onwards, asylum numbers increased steadily up to the 1950s despite big efforts of deinstitutionalization and the availability of psychological therapies. In 1950 the therapeutic effect of the first antipsychotic drug chlorpromazine was recognized [2]. This discovery led to a massive breakthrough in psychiatric therapy and to a drop of the residential psychiatric population in the United States of America (US) by 30% between 1955 and 1968 [3]. On top of that, chlorpromazine [2] and other new psychopharmacological drugs like the antidepressant imipramine [4, 5] allowed the mentally ill to live in their own homes and to obtain employment [3]. As those medications represented a massive achievement and helped with delusions, anxiety and low mood, they were also tried in patients with EDs, where these symptoms are highly prevalent [6, 7].

Because of anecdotal reports of success with antipsychotics, the use of first-generation antipsychotics to treat AN was investigated in open and uncontrolled, but also in randomized controlled trials (RCTs) in the 1970s and 1980s (for review see [7, 8]). Vandereycken [9] for example, reported a study using the antipsychotic sulpiride. In this RCT sulpiride was superior to placebo in terms of weight gain during the acute treatment period; however, it did not have any significantly beneficial effect on anorexic psychopathology such as anxiety and body image disturbances [9].

Regarding tricyclic antidepressants (TCAs), similar results were obtained from studies performed in the 1970s and 1980s [10, 11] (for review see [7, 8, 12]). Biederman et al. [10], for instance, reported a study comparing the effects of amitriptyline and placebo on weight gain and psychiatric symptomatology with no significant differences between the two groups except for more adverse effects in the amitriptyline group. Even though there were also few positive reports about the use of TCAs [13], the overall impression was that treatment with first-generation antipsychotics and TCAs could not be recommended [7] due to a lack of evidence and a high dropout rate in patients receiving these medications. Hence, these psychopharmacological agents did not gain general acceptance for the treatment of EDs at that time; and it seemed like patients with EDs could not benefit from the great breakthrough psychopharmacological therapies had achieved in other areas of psychiatry.

Between the 1980s and today, the situation changed due to diagnostic and psychopharmacological advances. In terms of diagnostic categories, bulimia was included into the DSM-III in 1980 [14] after the description of “bulimia nervosa” by Gerald Russell [15]; and in 2013, DSM-5 introduced BED as a separate disorder [16]. Regarding new psychopharmacological developments, the selective serotonin reuptake inhibitor (SSRI) fluoxetine came into the market in 1986. It was tested in patients with BN yielding positive results [17] and approved by the US Food and Drug Administration (FDA) in 1987. Since then a large amount of evidence has been collected [18-22], fluoxetine is now the first-line psychopharmacological treatment for BN [23]. The psychopharmacological advances on the

basis of the introduction of SSRIs into the market are reflected by a Cochrane Review which revealed that patients treated with TCAs dropped out of RCTs more frequently than patients treated with placebo, but that the opposite was found for those treated with the SSRI fluoxetine, suggesting fluoxetine is a more acceptable treatment [24]. Additionally, another systematic Cochrane Review demonstrated that combination treatments using psychotherapy plus an antidepressant in bulimia nervosa were superior to single psychotherapy [25].

In the 2000s and 2010s, the idea of treating EDs with antipsychotics was also revived, because second-generation antipsychotics became available. For example, an increasing amount of evidence has been gathered from RCTs [26-29] (for review see [30]) and clinical observations (for example [31]) showing that olanzapine may be helpful to treat symptoms of AN.

On top of these pioneering diagnostic and therapeutic advances, there was significant progress in other research areas such as epidemiology and comorbidity research [32-40], genetics [41-51], research on neural circuits and neurotransmitters [52-83] and on hormonal appetite regulation [84-87]. The results obtained in these research fields of the last few decades led to a deeper understanding of the biology of EDs.

## 1.2. Aim of this review

In this review article, we summarize novel clinical and epidemiological data, outline genetic and neurobiological advances, and comment on possible future translational and personalized approaches. The most important aim of this article is to bring together the results of pharmacological research, brain imaging and RCTs to develop a hypothetical model of where drugs for EDs act in the brain (see **Figure 1**). We think that this hypothetical model summarizes decisive scientific findings related to the psychopharmacological treatment of EDs, helps to understand the bigger picture of how medications can influence the brain on a molecular and functional level, and thus may facilitate the scientific discussion and the communication between clinicians, patients and carers about this important clinical topic.

As typical antipsychotics and TCA have not gained acceptance for the treatment of EDs, we don't include these studies into the main reasoning of this paper, but refer to previous research articles and reviews.

## **2. Eating Disorders**

### 2.1. Diagnostic considerations

EDs are characterized by a persistent disrupted eating behavior which leads to changes in the dietary intake, impaired physical health and psychosocial problems. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) currently recognizes three primary EDs: anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) [16]. Additionally, the DSM-5 mentions avoidant/restrictive food intake disorder (ARFID; an eating disturbance manifested by a restrictive eating pattern with persistent failure to meet appropriate nutritional needs), pica (the consumption of non-food) and rumination disorder (regurgitation and re-chewing food) [16]. For these latter three disorders there are no psychopharmacological RCTs reported in the literature as yet.

Within the EDs, clinical features can change over time, a proportion of patients with AN transition to BN and BED, and additionally, people with EDs, specifically BED can develop obesity. Overall, about one-half of patients with BED are obese [88] with obesity prevalence increasing over time from about 20% at baseline to about 40% five years later [89]. There are also a large number of patients with obesity who report binge eating with percentages ranging from 12% to 78% according to the degree of severity [90-93]. In individuals who seek weight control treatment the prevalence of BED is about 30% [93]. Obesity, however, is not considered an ED in DSM-5, even though there was a proposal to do so [94].

## 2.2. Anorexia nervosa

The prevalence of AN is approximately 1-4% among women, but lower in men with a sex ratio of men to women of about 1:10 [32, 33]. The peak incidence is at an age between 14 and 17 years [34]. AN is frequently associated with depressive disorder [36], obsessive compulsive disorder (OCD) and autism spectrum disorder [37]. The course is often chronic and it can lead to persistent disability [95]. A recent longitudinal cohort study showed that about 30% of patients with AN have recovered after 9 years and about 60% after 22 years [1]. The main criteria for the diagnosis are a significantly low body weight in the context of age, sex, and physical health, intense fear of weight gain and disturbed body perception [16]. The dietary deficit is often accompanied by significant physical health issues such as growth retardation, osteopenia, amenorrhoea and renal insufficiency, but also changes in laboratory parameters, cardiac arrhythmia and disturbances of the thyroid function [96]. The most common causes of death in patients with AN are sudden cardiac death associated with ventricular arrhythmias and suicide [97-99]. An overview on the prevalence, diagnostic criteria, and frequent psychiatric comorbidities for each ED is provided in **Table 1**.

## 2.3. Bulimia nervosa

BN occurs in 1-2% of women with a sex ratio of men to women of about 1:10 which is comparable to AN. The peak age is between 20 and 30 years [33, 34]. BN is often associated with affective disorders [36], impulse control disorders, attention deficit/hyperactivity disorder (ADHD), drug dependence, anxiety disorders, dissociative disorders, and the mental consequences of childhood trauma [36, 38, 39]. The main criteria for the diagnosis of BN are recurrent binges (the consumption of an unusually large amount of food within a short time interval associated with loss of control) associated with compensatory behaviors such as vomiting, excessive physical activity or fasting at least once a week for three months and excessive preoccupation with shape and weight [16].

## 2.4. Binge Eating Disorder

BED is the most prevalent EDs and can lead to reduced social and emotional functioning, quality of life, productivity and health impairments. Many patients are unaware that it is a recognized form of EDs and present for treatment for weight-related issues or comorbid medical and psychiatric conditions such as affective and anxiety disorders [35, 40]. BED is about twice as frequent as BN (between 2 and 5% of the population) with the proportion of women being about 60% among patients with BED [33]. BED is characterized by the intermittent consumption of large quantities of food (binge eating) at least once a week for three months without the use of the extreme compensatory strategies such as purging used in BN [16].

## 2.5. The spectrum of eating disorders

Given that transitions between diagnostic categories are common, some theorists have proposed dimensional models of EDs or - in other words - a spectrum of disordered eating. This view is supported by the fact that there are many overlapping risk factors and symptoms [94, 100-104].

## 2.6. Preliminary remarks regarding psychopharmacological treatment

Psychological therapies are currently the main treatment strategies for AN, BN and the BED. Only few psychopharmacological agents have been approved for EDs in some countries. We have already highlighted the high comorbidity at a symptom or syndrome level with affective disorders, anxiety disorders, autism, OCD, ADHD, and substance-related disorders [36-42]. Therefore it stands to reason that medication approved to treat these highly comorbid conditions might also be useful in the treatment of EDs. Moreover, comorbidities might help to define specific subgroups of patients suffering from EDs and to develop individually tailored drug therapies to treat the ED. Even though the current literature doesn't allow such far reaching conclusions, comorbidities might help specify the disturbed neural circuits underlying the ED in an individual patient, as we will explain below.

## **3. Biological findings in patients with eating disorders**

### 3.1. Genetics

The familial nature of AN has been well established; the first-degree relatives of individuals with AN have approximately a tenfold greater lifetime risk of falling ill with an ED than relatives of unaffected individuals [41-44].

However, family studies are unable to determine the extent to which the observed familial aggregation is due to genetic or environmental factors. To determine the genetic risk, twin studies have been performed, which have yielded a high heritability of 50-60%; for example, a large twin study performed by Bulik et al. [41] led to a heritability estimation for AN of 56%, with the remaining variance attributable to shared environment and unique environment.

The genetic liability to AN is, like other complex disorders, thought to consist of many genetic variations of small effect identified by genome wide association study (GWAS) techniques [45-47]. In a GWAS reported by Duncan et al., however, the authors identified one genome-wide significant locus on chromosome 12 in a region harboring a previously reported type 1 diabetes and autoimmune disorder locus [47]. Genetic studies using state-of-the-art technologies in BN or BED are limited [48], and to our knowledge no large GWAS have been performed in BN and BED yet.

The so-called LD score regression (LDSR) has been used to estimate the shared genetics (genetic covariance from GWAS studies) between disorders. This has revealed significant positive genetic correlations between AN and OCD, schizophrenia and neuroticism [47, 49, 50]. Additionally, there are genetic correlations with somatic and metabolic features including specific insulin, glucose, and lipid phenotypes and a significant negative correlation

between the body mass index (BMI) [47, 49, 50].

BMI related genes such as the polymorphism of the fat mass and obesity-associated (FTO) gene have also been found to be associated with BED [51]. Thus disorders with loss of control over eating seem to share a similar genetic profile to obesity.

These genetic findings suggest that EDs like AN and BED may not only be psychiatric disorders or – in other words – disorders of the brain, but also metabolic or immune disorders. Moreover, the mentioned novel genetic data could mean that there are different subtypes of EDs, for example a psychological, a metabolic and an immune subtype of AN. This development could change the way we see and treat EDs, because immunological and metabolic messenger molecules like cytokines and hormones may play important roles as drug targets for EDs in the future.

### 3.2. Neural circuits and neurotransmitters

Appetite control includes a complex integration of several neural circuits including those related to (1) self- and social regulation, learning and memory, (2) hedonic aspects associated with the desire to eat and pleasure during food consumption and satiation, and (3) the homeostatic regulation which integrates peripheral signals of food consumption and energy stores with central systems of appetite control [52-58]. These neural circuits are both anatomical and functional entities. On the basis of the current literature we propose a model in which we allocate certain brain functions, anatomic structures, their input and signal molecules, associated comorbidities and psychopharmacological agents to these three systems, the self-regulatory, the hedonic and the homeostatic system [52]. However, this is only an attempt to classify comorbidities and medications according to the putatively most relevant neural circuits for EDs. We are aware that this model includes several simplifications, but it helps to understand the role of the most important neural circuits and their signal molecules in EDs in keeping with the latest research. For further information regarding these three systems see **Table 2**.

The *self-regulatory system* which is mainly located in the prefrontal cortex embeds eating into the social context, forges individual values and self-regulatory control by incorporating social, cultural and environmental factors through learning for which the neurotransmitters serotonin, serotonin (5-HT), norepinephrine (NE), acetylcholine (ACh) and dopamine (DA) play an important role [52-60]. These neurotransmitters have been shown to be involved in mood disorders, OCD, anxiety disorders, personality disorders, neuroticism and schizophrenia. Therefore, medications that play a role in these disorders like antidepressants, antipsychotics, glutamatergic agents and anti-dementia drugs could be considered to influence this system and therefore to be potentially useful in the treatment against EDs as we will explain in detail later. We are not aware of any scientific literature on cognitive enhancers for the treatment of EDs. However, one single anti-dementia drug has been theoretically considered [105]. The self-regulatory system seems to play a decisive role in the pathophysiology of BN, as a functional magnetic resonance imaging studies found abnormal patterns of activation in frontal systems which are important for the regulatory control of food intake [106, 107]. These divergent activation patterns may be responsible for the inability of patients with BN to control conflicting desires to consume fattening foods on the one hand and to avoid weight gain on the other hand [106].



Neural reward dysfunction in the *hedonic system* may underpin dysfunctional eating behavior in AN, BN and BED with anorexia nervosa associated with too little striving for reward and binge eating too much [55-64, 108]. Prefrontal areas, particularly the orbitofrontal cortex (OFC) and corticostriatal circuits including the nucleus accumbens play an important role in reward processes [64-67]. A recently proposed bio-psycho-social model suggests that in AN there is a hypersensitivity to food stimuli, whereas there may be a desensitization to food stimuli specific in BN, BED and obesity) [66, 67]. Being sated or hungry, or being underweight or overweight is associated with heightened or reduced brain reward response in the insula, the subcortical ventral striatum, and the prefrontal cortex [67]. A number of different neural messenger molecules such as endogenous opiates and cannabinoids and dopamine are involved in the reward system [68-72]. Opiate agonists, inverse agonists and antagonists such as naltrexone, naloxone, nalmefene and GSK1521498 have all been found to influence eating behavior and the hedonic value of foods [68-72]. The hedonic system is additionally modulated by peripheral hormones involved in appetite regulation such as ghrelin and leptin [73, 74]. Several studies have provided evidence for altered patterns of hedonic system activity associated with reward processing in acutely ill patients with AN and recovered individuals [109]. Patients with AN show less hedonic response to eating, but consider behaviors like self-starvation – which are considered aversive and punishing in healthy people – more rewarding than eating [109]. On the contrary, subjects with BED show higher scores of hedonic eating compared to healthy controls [110].

The hypothalamus plays a central role in the *homeostatic system* regulating of food intake and body weight. It integrates signals about the nutritional state and food supply from the periphery and modulates food intake and energy consumption [75, 76]. An important orexigenic signal leading to hunger and food intake is ghrelin which is produced in the stomach [77]. Anorexigenic signals from the body periphery include glucose, the enterocyte hormone glucagon-like peptide-1 (GLP-1) [78], the pancreatic hormone insulin and the fatty tissue hormone leptin [76]. In the hypothalamus, the arcuate nucleus, the paraventricular nucleus and the lateral hypothalamus are of particular relevance for weight regulation [76, 79]. The arcuate nucleus integrates the incoming humoral signals of GLP-1, insulin, leptin, ghrelin and other hormones and energy carriers such as glucose and converts them into neuronal signals. Orexigenic hypothalamic signalling molecules are NPY and AgRP which lead to an increase in appetite, while  $\alpha$ -MSH as well as cocaine and amphetamine regulated transcript (CART) are anorexic signals which lead to a feeling of satiety [76].  $\alpha$ -MSH is produced by the so-called pro-opiomelanocortin (POMC) neurons. [80]. In acute episodes of AN, for example, ghrelin has been found to be overexpressed, and leptin reduced as would be expected in starvation [96]. However, plasma levels of NPY (part of the orexigenic system) are anomalously low [96]. Abnormalities within the hormonal regulation of the homeostatic system have also been reported for BN [111] and BED [112].

Within the arcuate nucleus, orexigenic factors increase hypothalamic adenosine monophosphate-activated protein kinase (AMPK) activity which is an intracellular appetite signal leading to food intake [79, 80]. This homeostatic system is modulated by neurotransmitters of the hedonic system (cannabinoids, endogenous opioids and dopamine) as well as signaling molecules of the self-regulatory system like serotonin, norepinephrine, glutamate, and acetylcholine [81-83]. Histamine plays a central role in the homeostatic system itself, as we will explain in the next paragraph. **Figure 1** depicts a simplified

overview of the interplay of these appetite-regulating molecules within the three systems, the *homeostatic system*, the *self-regulatory* and the *hedonic system*.

The atypical antipsychotic olanzapine, an antagonist at serotonin and dopamine receptors, is of interest as a treatment option for AN [26-31, 113]. It has been reported to lead to weight gain in patients with schizophrenia [114] on the basis of its high affinity towards the histaminergic H<sub>1</sub> receptor and its antihistaminergic action [115]. The antihistaminergic effects of olanzapine at the H<sub>1</sub> receptor leads to an increase of the hypothalamic AMPK activity. Therefore, the antihistaminergic effect of olanzapine could be beneficial in the treatment of an ED like AN, where weight gain is intended. It has to be mentioned though that neurotransmitters and hormones which belong to the homeostatic system like insulin, leptin and ghrelin play important roles in food reward [73-76, 84, 85] which is an example how the three systems – the self-regulatory, the hedonic and the homeostatic system – influence each other and should therefore not be considered as separate from each other.

### 3.3. Hormones

Hormones like sex steroids also influence eating behaviour significantly. Human epidemiological and experimental animal studies have shown that, for example, oestrogens display a key role in the control of food intake and energy balance [87]. Furthermore, the lack of oestrogens causes impaired bone health in AN [116]. Another hormone which could be relevant in the development of EDs is the neuropeptide hormone oxytocin which has been shown to inhibit food intake and to increase energy expenditure in animals [117, 118]. It is released into systemic circulation in situations of psychosocial interaction, and has been shown to be involved in mechanisms of social bonding and social recognition [117, 118], areas where patients with AN show specific difficulties [119], and to be a possible mediator of SSRI-induced antidepressant effects [120].

## **4. Psychopharmacologic advances in anorexia nervosa**

A primary goal of RCTs to test medication in AN is the restoration of body weight or the stabilization of body weight after weight restoration. However, even though professionals and carers usually agree upon this treatment goal, a recent survey among AN patients and carers reveals that people with anorexia nervosa themselves want medication to help with anxiety and sleep problems [121], but doubt that psychopharmacological drugs can help with AN. This divergence in aims may account for poor take up and adherence [8, 30,] in pharmacological studies which has impeded developments in the field.

Currently discussed psychopharmacological agents to treat for AN include atypical antipsychotics, the cannabinoid receptor (CB) agonist dronabinol and D-cycloserine [30]. A recent systematic review to summarize evidence from research on psychopharmacological options for adult patients with AN [8], however, came to the conclusion that the body of evidence for the efficacy of pharmacotherapy in AN was unsatisfactory, because the quality of observations was questionable, and sample size was often small. Nevertheless we will discuss the most promising developments.

### 4.1. Antipsychotics

According to the mentioned current review to identify recent developments in the pharmacotherapy of eating disorders [30] and a recent meta-analysis [113], olanzapine is the most promising drug for patients with AN, because with regard to weight gain it was superior to placebo in four published RCTs [26-29], and in a not yet published but recently completed large, multisite RCT in patients with anorexia nervosa performed by Attia et al. [30]. In these studies, body weight gain was the major outcome measure. As olanzapine impacts serotonergic, dopaminergic and histaminergic neurotransmission, it could have impact on the self-regulatory, the hedonic and the homeostatic system. Through its antihistaminergic activity, olanzapine may also help patients with their anxiety [122] and sleep problems [123]. Previous studies [26-29] initiated olanzapine treatment at 2.5 mg/d and increased this dose slowly to 5 mg or 10 mg/d. This dosage is within the British National Formulary (BNF) limits [124], but at the lower end. As BNF cites caution for people with a slower metabolism and female patients, we recommend a slow up-titration schedule (2.5 mg/d increments each week up to a maximum of 10 mg/d), and the same down-titration increment at the end of treatment to improve patient safety.

A few case reports suggest that aripiprazole - a partial dopamine agonist – may also be effective in the treatment of AN [125-127]. In a chart review of 75 patients with AN who received either olanzapine or aripiprazole, aripiprazole showed the greatest effectiveness in reducing eating-related preoccupations and rituals with a large effect size [128]. In the literature [125-127], relatively small doses were used. For example, in a case series published by Trunko et al. [125] patients received aripiprazole doses of between 5 and 15 mg/d.

4.2. Dronabinol (cannabinoid receptor agonist): Dronabinol is a synthetic form of delta-9-tetrahydrocannabinol (THC) acting on CB1 and CB2 [129]. It is available for the treatment of cachexia in tumour and HIV infected patients [130]. A small study (n=25) found that patient with AN who were treated with dronabinol showed an greater weight gain compared to placebo [131].

4.3. D-cycloserine (NMDA receptor agonist): D-cycloserine is a glutamatergic partial agonist at the glycine/D-serine site on the (N-methyl-D-aspartate) NMDA receptor, which is a subtype of glutamate receptors [132]. In a recently published trial with 36 patients with AN in which participants were randomly assigned to receive exposure therapy plus D-cycloserine or placebo, participants in the D-cycloserine group showed a significantly greater increase in BMI than those in the placebo group. D-cycloserine participants gained 3 pounds relative to 0.5 pounds in the placebo group [133]. However, from this study, it can only be concluded that D-cycloserine improves the results of exposure therapy for AN, but not that it would lead to weight gain by itself in this patient group. Therefore, it may be one of the drugs which could rather be recommended to sustain normal weight after weight restoration or to enhance the effects of psychotherapy.

These preliminary proof-of-concept studies suggest that olanzapine [26-29], aripiprazole [126-128] or dronabinol [131] may have promise (see **Figure 1**). However, for the moment any use of medication for AN itself would be considered off-label use, although medications for comorbidities (depressive or obsessive compulsive disorder) are commonly prescribed.

## 5. Psychopharmacologic advances in bulimia nervosa

In contrast to AN, the clinical use of medications in the treatment of BN has been well established [12, 30], and the SSRI fluoxetine has long been approved for the treatment of BN. RCTs usually aim to reduce binge and purge behaviour as main outcome parameter. As systematic reviews and guidelines have already summarized the results of RCTs in BN for antidepressants, antiepileptics, lithium and other drugs [12, 23], we will mainly focus on fluoxetine and topiramate, because these drugs appear as the treatment options supported by the most evidence.

### 5.1. Serotonergic antidepressants

The serotonergic agent fluoxetine which also influences NPY and POMC neurons in the hypothalamus [134] has a strong evidence for acute and maintenance treatment [17-22]. Fluoxetine should be started at a dose of 20 mg/d and increased to a dose of 60 mg/d. 60 mg/d is the dose evaluated in both acute and recurrent prophylaxis with high evidence of clinical efficacy and a good benefit-risk profile. The dose of 60 mg/d is more effective than lower doses [23, 124, 135]. The positive effect on the number of binges seems to be independent of its antidepressant effect. Therapy length of two years is recommended [135].

### 5.2. Topiramate (glutamatergic agent)

The anti-epileptic drug topiramate interacts with voltage-gated calcium channels and thereby modulates glutamate levels and inhibits kainate-mediated conductance at glutamate receptors of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate type [136, 137]. Therefore, we consider topiramate a glutamatergic agent. Additionally, it increases leptin, insulin and  $\alpha$ -MSH production [138]. It has been shown to be effective at reducing binge eating and self-induced vomiting in BN and is well-tolerated, in several RCTs. For example, in studies published by Hoopes et al. and Hedges et al. [139, 140] topiramate led to significantly greater reductions than placebo in the number of binge/purge days, in body dissatisfaction and drive for thinness. Abstinence rates from binge-eating and purging were 23% for topiramate and 6% for placebo. Topiramate was associated with significant reductions in anxiety, and participants on topiramate lost significantly more weight than the placebo group, who tended to gain weight [139, 140]. Important side effects were tiredness as well as cognitive and mnemonic disturbances. Topiramate is currently under scrutiny at the FDA for approval for bingeing and purging behaviour in BN and BED in a fixed combination with the stimulant phentermine. Topiramate treatment should start at 12.5 or 25 mg/d and increased very slowly to between 75 and 200 mg/d [124, 135] to avoid cognitive and mnemonic side effects. Positive effects on binges and self-induced vomiting have been found in several RCTs. However, it is still not approved for the treatment of BN and therefore its use in BN is off-label.

### 5.3. Others

The serotonergic drug ondansetron showed a positive effect in several RCTs such as an RCT performed by Faris et al. [141], but cannot be recommended as an off-label indication for BN due to the risk of a dose-dependent prolongation of the QTc interval [142]. Naltrexone an antagonists at the  $\mu$ -opioid receptor, the  $\kappa$ -opioid receptor and the  $\delta$ -opioid receptor [143] has shown inconsistent results in BN, and the studies performed so far have low statistical power

[23]. In two small open trials, bulimic symptoms decreased significantly under treatment with naltrexone [144, 145]. Naltrexone, could represent a future psychopharmacological advance, if appropriately designed large studies will replicate the reported positive effects.

## 6. Psychopharmacologic advances in binge eating disorder

As BED is a relatively novel diagnosis [16], the number of RCTs testing psychopharmacological approaches for BED is limited. So far, main outcome criteria have been a reduction of binges and body weight [146-148].

### 6.1. Stimulants

Lisdexamfetamine (LDX) is a prodrug of amphetamine which influences the *hedonic system* and also up-regulates CART expression in animal models [149, 150]. It was already approved for treatment of children and adults with ADHD. LDX is the only drug approved by the FDA for the treatment of moderate to severe BED in adults. However, it is only approved in the US; its use in other countries is still off-label. The approval was based on three studies which found LDX superior to placebo for reducing binge eating days, obsessive-compulsive binge eating symptoms, and body weight, and for inducing 4-week binge eating cessation rates [146-148]. The approval of LDX by the FDA in 2015, the same year as BED was acknowledged as an independent diagnosis in the DSM-5 [16], definitely represents a major advance in the psychopharmacological treatment of eating disorders. In a recent safety and tolerability trial, there was a four weeks initial titration dose which started at 30 mg/d LDX; the target and maintenance doses were between 50 and 70 mg LDX given over 48 weeks [151]. This approach is in keeping with the previous literature about LDX in patients with BED [146-148].

### 6.2. Others

Drugs used for obesity may also reduce weight in BED as there is a significant overlap between both diagnoses [88-94]. Therefore, we would like to briefly mention these drugs as well, even though they are not yet tested for BED but only for obesity. Liraglutide is an analogue of the anorexigenic bowel hormone GLP-1 which binds to the GLP-1 receptors in the hypothalamus. It has been shown to lead to significant weight loss in obese patients and to an improvement regarding the various health consequences of obesity in a number of RCTs [152-157]. Two RCTs with naltrexone plus bupropion showed superior weight outcomes to placebo in patients with obesity with no adverse effects [158, 159]. This combination is thought to lead to weight loss by modulation of opioid, dopamine and norepinephrine signaling in both the self-regulatory and the reward system. Further new pharmacological approaches for obesity include the norepinephrine reuptake inhibitor reboxetine [160], the monoamine reuptake inhibitor tesofesin [161], the CB1 receptor antagonist taranabant [162], the peptide YY3-36 [163] which is a product of enteroendocrine cells, the pancreatic and lipase inhibitor cetilistat [164]. From preclinical and healthy studies, there is also evidence for the efficacy of intranasal insulin to reduce appetite and food intake [165]. Furthermore, there is already sufficient evidence from RCTs for the beneficial clinical effect of the serotonin receptor agonist lorcaserin [166] and the combination of the stimulant phentermine which has similarities with amphetamine plus topiramate [167-170].

## 7. Discussion

### 7.1. Psychopharmacological advances in EDs

In AN, the reports of weight gain under the treatment with olanzapine [26-29], aripiprazole [125-128] or dronabinol [131] can be considered as psychopharmacological advances. As topiramate [139, 140] led to reductions in the number of binge/purge days, in body dissatisfaction and drive for thinness, it seems to be a promising novel development in BN. The approval of LDX for BED after convincing positive RCTs [146-148, 151] definitely represents a major advance in the psychopharmacological treatment of eating disorders.

Apart from RCTs, there has also progress been made with regard to the understanding of where and how medication for EDs may work on a molecular level and thus influence important neural circuits. The results of these non-clinical studies encouraged us to formulate a comprehensive pharmacodynamic model which includes as major players signal molecules and receptors of the self-regulatory system such as serotonin, norepinephrine, acetylcholine and glutamate, of the hedonic system including opioids, cannabinoids and dopamine and of the hypothalamic homeostatic system including histamine, ghrelin, leptin, insulin, glucagon-like peptide-1 (see **Figure 1**). Even though this model represents a simplification of study results, we hope that it helps to see the bigger picture of how psychopharmacological medication may be able to influence the brain for the benefit of patients with EDs.

### 7.2. Critical remarks

As already stated by several meta-analyses, systematic and narrative reviews [7, 8, 12, 23, 24, 30] the majority of studies for drug treatment in EDs are small, and the study design across the studies is heterogeneous. We tried to draw conclusions about the most important drugs discussed in our article on the basis of meta-analysis and systematic reviews. However, for some promising medications like aripiprazole or dronabinol, there are no such articles available. Additionally, EDs are complex phenotypes with a variety of psychological and physical symptoms within one diagnostic category. In this article, however, we only resorted to the treatment of the whole disorder. Thus, we did not go into detail with regard to specific symptoms like ED-specific cognitions, hyperactivity or non-occurrence of menstruation. These are symptoms that could also be targeted pharmacologically. For example, current reports suggest the potential of leptin to treat hypothalamic amenorrhea in female patients [171] or anorexia based activity in rats [172]. Moreover, in order to focus on the attempt to classify medication according to their primary target location, we have given little attention to adverse effects.

Drug treatment is set within the context of a wider treatment plan including psychotherapy, family therapy, diet counselling, occupational therapy and physiotherapy. However, space was too limited reflect on the interaction of these psychological interventions and drug treatment.

Throughout our article, we focused more on problematic energy intake and eating behavior in EDs than on energy expenditure which is also regulated within the central nervous system and could therefore be tackled using psychopharmacological agents. Furthermore, peripheral molecular structures like the sirtuins which regulate cellular metabolism and mitochondrial

function might also be important for weight regulation [173].

Our article is lacking a comprehensive synopsis of neuroendocrine findings which would potentially help to identify potential drug targets particularly in AN - e.g. low gonadotropin levels, high ghrelin levels and low leptin levels. For a compilation of these changes in laboratory parameters from our perspective, we recommend reading our previous article [96].

### 7.3. Future perspectives

A more individualized approach based on biomarkers or neuropsychiatric findings could improve efficacy, effectiveness and adherence in psychopharmacological treatment for EDs. We have already highlighted the high comorbidity at a symptom as well as syndrome level with affective disorders such as depression, anxiety disorders, autism, OCD, ADHD, and substance-related disorders [36-40] and the positive genetic correlations between AN and OCD, schizophrenia and neuroticism [49, 50]. Therefore, approved treatment for these epidemiologically as well as biologically related disorders could be considered for EDs as well. Broadly speaking, current and future drugs used in other psychiatric disorders could be used in related EDs as well. Examples are LDX, essentially a long-acting D-amphetamine which is approved for the treatment of patients with ADHD, or fluoxetine which is an SSRI that has been used as a psychopharmacological drug for depression and OCD. We further assume that considering the associated disturbances in the underlying neural circuits might lead to a deeper understanding of the similarities between these disorders and EDs and therefore fertilize novel psychopharmacological approaches or improved combinations of psychotherapy and pharmacotherapy.

## **8. Expert Commentary**

Current treatment outcomes for all EDs are poor. Outpatient interventions usually fail to achieve weight restoration in the vast majority of AN patients [174], only about 30% of patients with AN have recovered after 9 years [1] and patients with BED remain obese. Therefore, there is an urgent need for novel treatment options.

One approach would be to look at comorbidities such as depression, anxiety, ADHD, OCD and schizophrenia. These comorbidities might give a hint about the underlying disturbed neural circuits. For example, a patient with BN, OCD symptoms and depression may most likely profit from an SSRI like fluoxetine, because there might be a serotonin-related disturbance in the self-regulatory system which leads to three different symptom patterns.

This thought about comorbidities could also have relevance for future RCTs. For example, patients with AN and delusional symptoms might rather profit from an antipsychotic, and patients with AN and OCD might more likely improve during treatment with a serotonergic antidepressant. Therefore, to look at the comorbidities might help to create subtypes of patients, and to treat them in a more individualized way. It may well be that the low success rate in RCTs is due to the heterogeneity of patients, and that a more individualized approach would be more effective.

Other novel approaches could be drugs which improve social relationships or learning to enhance the effects of psychotherapy for EDs. In this respect, we would like to refer again to

oxytocin [117-120] and D-cycloserine [133].

In view of future advancements in the pharmacotherapy of EDs, it may be useful to think about how medications could influence and treat psychopathological features, symptoms, emotional states and specific behaviors associated with EDs instead of treating comorbidities or the ED as a whole. Those emotional states and behaviors could relate to anxiety, anger, low self-esteem, self-criticism, asceticism, problems of social-emotional functioning, and suicidal and self-injurious behaviors. Psychopharmacological agents targeting specific psychopathological features, ways of behavior and emotional states should therefore be considered when planning future RCTs in patients with EDs. At this point, it is worth mentioning that patients and carers particularly like this approach of using medications to tackle specific symptoms such as anxiety [121].

However, one main concern from our clinical experience is that many patients with AN refuse drug treatment, because they are afraid of weight gain. Therefore, compliance and adherence remain key problems for the treatment of EDs and require a high level of clinical expertise. In future research, the inclusion of Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) into the outcome criteria for RCTs in EDs should be considered in order to make the participation in RCTs more attractive for patients with EDs [121]. PROMs and PREMs have already been developed within the National Health Service (NHS) of the United Kingdom (UK) for certain elective surgery procedures [175], but not yet for the psychopharmacological treatment of AN. If the main outcome criteria of an RCT were to include PROMs and PREMs regarding, for example, anxiety in addition to BMI changes, the RCT would be of benefit from a patients' perspective and may improve the willingness to participate in the RCT [121].

## 9. Five-year view

The latest genetic findings suggest that EDs may not only be seen as psychiatric, but also as metabolic or immune disorders, and that there may be different subtypes of EDs like a psychological, a metabolic and an immune subtype of each ED. In five years' time we may be able to postulate those biologically distinct subtypes of EDs.

Genetic research has linked EDs with disorders of the immune system [47]. These results are supported by anomalies in the cytokines system reported in patients with EDs [96, 176, 177]. Messenger molecules of the immune system may be promising future drug targets for EDs as they are significantly involved in appetite regulation [96, 178, 179]. The immunological perspective may also become interesting when taking into account the gastrointestinal microbiome and its interactions with diet, inflammation, and epigenetic alterations. Probiotics and bioactive nutrients have been shown to alter this microbiome as well as immune and brain function [180] and could therefore have therapeutic potential to influence appetite regulation and ED psychopathology [181]. Future genetic research in EDs may not only take human genes, epigenetics and gene expression, but also the genes of bacteria, fungi and other species living in the human body into account. Therefore, we assume that the next few years will unveil drug targets for EDs not just outside of the brain, but possibly even outside of our body, if we consider our intestinal tract as an external surface.



## 10. Key issues

- The only approved psychopharmacological treatment options for EDs to date include fluoxetine for BN and lisdexamfetamine for BED.
- Evidence derived from RCTs suggests that olanzapine may be helpful to treat symptoms of AN.
- Given the high comorbidity with other psychiatric disorders, novel medications for these conditions might also be effective in EDs.
- Currently discussed psychopharmacological medications for EDs influence three important neural circuits of the brain: the self-regulatory system, the hedonic system and the hypothalamic homeostatic system.
- Drug targets for the treatment of EDs include molecules of the serotonin, norepinephrine, dopamine, histamine, glutamate, opioid and cannabinoid system as well as the hormones ghrelin, leptin, insulin and GLP-1.
- Genetic research suggests that EDs should not only be perceived as disorders of the brain, but also as immune or metabolic disorders. Therefore, future pharmacological agents for EDs may primarily influence the immune system or metabolic processes of the body.
- The microbiome seems to be an additional promising future drug target.
- PROMs and PREMs should be inserted into the outcome criteria for RCTs in EDs.

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\*\* Superb and innovative opinion piece about the relations between the microbiome, microbiota and AN.

**Table 1:** Prevalence, decisive diagnostic criteria and frequent psychiatric comorbidities. Abbreviations: Obsessive-compulsive disorder (OCD), attention deficit/hyperactivity disorder (ADHD). For further details see text.

<b>Eating disorder</b>	<b>Prevalence</b>	<b>Diagnostic criteria</b>	<b>Frequent psychiatric comorbidities</b>
Anorexia nervosa	<ul style="list-style-type: none"> <li>• 1-4% among women</li> <li>• Sex ratio men/women: 1/10</li> </ul>	<ul style="list-style-type: none"> <li>• Significantly low body weight</li> <li>• Intense fear of weight gain</li> <li>• Disturbed body perception</li> </ul>	<ul style="list-style-type: none"> <li>• Depressive disorder</li> <li>• OCD</li> <li>• Autism spectrum disorder</li> </ul>
Bulimia nervosa	<ul style="list-style-type: none"> <li>• 1-2% among women</li> <li>• Sex ratio: 1/10</li> </ul>	<ul style="list-style-type: none"> <li>• Recurrent binges</li> <li>• Compensatory behaviors</li> <li>• Self-evaluation unduly influenced by body shape and weight</li> </ul>	<ul style="list-style-type: none"> <li>• Affective and anxiety disorders</li> <li>• Impulse control disorders</li> <li>• ADHD</li> <li>• Addictions</li> <li>• Dissociative disorders</li> <li>• Childhood Trauma</li> </ul>
Binge eating disorder	<ul style="list-style-type: none"> <li>• 3% of the population</li> <li>• Sex ratio 1/3</li> </ul>	<ul style="list-style-type: none"> <li>• Binge eating</li> <li>• No extreme compensatory strategies</li> </ul>	<ul style="list-style-type: none"> <li>• Affective disorders</li> <li>• Anxiety disorders</li> </ul>

**Table 2.** Brain systems involved in the pathophysiology of EDs. This table attempts to categorize brain functions, anatomical structures and signal molecules in a simplified way, but in keeping with the current literature – according to the three arguably most relevant neural circuits: the self-regulatory, the hedonic and the homeostatic system. Abbreviations: Serotonin (5-HT), norepinephrine (NE), acetylcholine (ACh), dopamine (DA), neuropeptide Y (NPY), agouti-related peptide (AgRP), melanocyte-stimulating hormone ( $\alpha$ -MSH), cocaine and amphetamine regulated transcript (CART), glucagon-like peptide-1 (GLP-1). For further details see text.

<b>Brain System</b>	<b>Self-regulatory system</b>	<b>Hedonic system</b>	<b>Homeostatic system</b>
<b>Functions</b>	<ul style="list-style-type: none"> <li>• Embedding eating into social context</li> <li>• Individual values</li> <li>• Self-regulatory control</li> </ul>	<ul style="list-style-type: none"> <li>• Desire to eat</li> <li>• Pleasure during food consumption</li> </ul>	<ul style="list-style-type: none"> <li>• Integration of peripheral signals of food consumption and energy storages</li> <li>• Appetite regulation</li> </ul>
<b>Anatomical structures</b>	<ul style="list-style-type: none"> <li>• Prefrontal cortex</li> </ul>	<ul style="list-style-type: none"> <li>• Prefrontal cortex</li> <li>• Basal ganglia</li> <li>• Thalamus</li> </ul>	<ul style="list-style-type: none"> <li>• Hypothalamus</li> </ul>
<b>Input</b>	<ul style="list-style-type: none"> <li>• Social and cultural factors</li> <li>• Environment</li> </ul>	<ul style="list-style-type: none"> <li>• Sensory organs</li> <li>• Hippocampus</li> </ul>	<ul style="list-style-type: none"> <li>• Peripheral signals of food consumption and energy storages</li> <li>• Self-regulation system</li> <li>• Hedonic system</li> </ul>
<b>Signal molecules</b>	<ul style="list-style-type: none"> <li>• 5-HT</li> <li>• NE</li> <li>• ACh</li> <li>• DA</li> </ul>	<ul style="list-style-type: none"> <li>• DA</li> <li>• Glutamate</li> <li>• Opioids</li> <li>• Cannabinoids</li> </ul>	<ul style="list-style-type: none"> <li>• Leptin</li> <li>• Ghrelin</li> <li>• Insulin</li> <li>• GLP-1</li> <li>• NPY</li> <li>• AgRP</li> <li>• <math>\alpha</math>-MSH</li> <li>• CART</li> <li>• Histamine</li> </ul>

**Figure 1:** Schematic and simplified depiction of the interplay of the hedonic system, the self-regulatory system, the homeostatic system, the body periphery and the molecular target location of selected promising medications to treat EDs. The potential indication is given in brackets. Abbreviations: Anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), opioids (Op), cannabinoids (CB), dopamine (DA), serotonin (5-HT), norepinephrine (NE), acetylcholine (ACh), glutamate (Glu), neuropeptide Y (NPY), agouti-related peptide (AgRP), melanocyte-stimulating hormone ( $\alpha$ -MSH), cocaine and amphetamine regulated transcript (CART), glucagon-like peptide-1 (GLP-1). For further details see text.

